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INGREZZA®
(valbenazine) capsules

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KINECT 4:

A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia

Marder SR, Singer C, Lindenmayer JP, et al.
J Clin Psychopharmacol. 2019;39(6):620-627.

Important Information

INDICATION & USAGE

INGREZZA® (valbenazine) capsules is indicated in adults for the treatment of tardive dyskinesia and for the treatment of chorea associated with Huntington's disease.

IMPORTANT SAFETY INFORMATION

Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

Please see Important Safety Information throughout and accompanying INGREZZA full Prescribing Information, including Boxed Warning.

Background: KINECT 3 pivotal trial

FDA approval of INGREZZA® (valbenazine) capsules was based on positive results from the KINECT 3 pivotal study. KINECT 3 was a phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study evaluating the efficacy and safety of INGREZZA 40 mg or 80 mg, administered once daily for the treatment of adults with tardive dyskinesia (TD).[1,2]

KINECT 3 study design included

- 6-week double-blind, placebo-controlled treatment period: Patients randomized 1:1:1 to INGREZZA 40 mg, INGREZZA 80 mg, or placebo[1,2]
- 42-week double-blind treatment extension period, for up to 48 weeks of treatment. Patients receiving placebo were re-randomized 1:1 to INGREZZA 40 mg or INGREZZA 80 mg[1,2]
- Patients initially randomized or re-randomized to the 80 mg group received 40 mg for the first week[2,3]
  - Investigators could decrease the 80 mg dose once at any time during the study due to tolerability. Patients were discontinued if the new dose was not tolerated
- 4-week washout, for a total duration of up to 52 weeks[1]

KINECT 3 primary endpoint and results

- Primary efficacy endpoint was change in AIMS dyskinesia score (sum of items 1–7) from baseline to Week 6 for INGREZZA 80 mg vs placebo[1,2,a]
- At 6 weeks, patients experienced a ~30% reduction in TD severity with INGREZZA 80 mg[1-3,*]
  - Mean change from baseline to Week 6 was –3.2 for INGREZZA 80 mg vs –0.1 for placebo ($P \leq 0.001$)[b]. Reduction in TD severity was also seen with INGREZZA 40 mg (–1.9, $P<0.01$)[c]
  - AIMS score reduction by ≥50% from baseline was observed in more patients taking INGREZZA vs placebo
- INGREZZA provided continued reductions in TD severity through 48 weeks with once-daily dosing[1,4]

*In a post hoc analysis of the primary efficacy endpoint of patients randomized to INGREZZA 80 mg at baseline through Week 6 (n=70).
[a]Videos were scored by blinded central AIMS video raters. Raters were blind to treatment and study visit.
[b]Dose that was statistically significantly different from placebo to control for multiple comparisons.
[c]Nominal *P* value when controlled for multiple comparisons.

KINECT 4 study objective

KINECT 4 was a phase 3, open-label study conducted to further evaluate the long-term safety and tolerability of INGREZZA 40 mg or 80 mg, administered once daily. In addition, long-term effectiveness of treatment was assessed.[5]

Study population

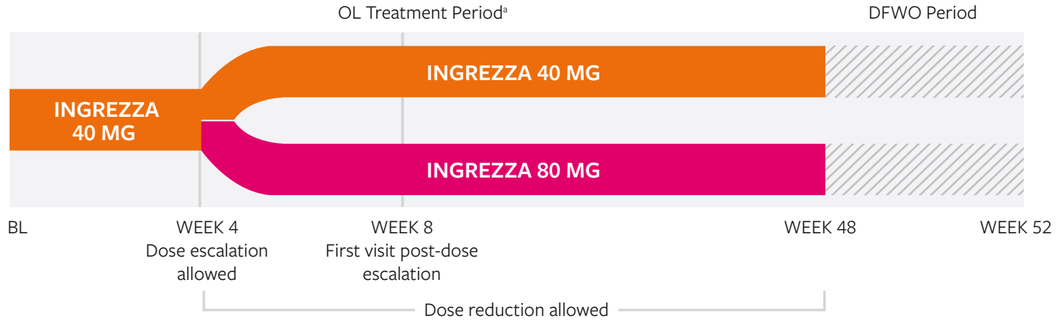
In this long-term, open-label study, INGREZZA was studied in a broad population of adult patients with various underlying diagnoses and treatment regimens.[5]

KEY INCLUSION CRITERIA	SELECT STUDY DEMOGRAPHICS
• Stable psychiatric status • 18 to 85 years of age	• Of the 167 participants who entered the study, 103 (61.7%) completed 48 weeks of treatment and a 4-week washout period • Mean age was 57.4 years of age
Patients had one of these diagnoses • Schizophrenia • Schizoaffective disorder • Mood disorder	• 73% had a diagnosis of schizophrenia or schizoaffective disorder • 27% had a mood disorder
Diagnosis of DRBA-induced TD for ≥3 months before screening • Moderate to severe TD based on qualitative assessment at screening	• 88.3% were taking antipsychotics • 65% were taking antidepressants • 27% were taking anticholinergics

DRBA, dopamine receptor blocking agent.

KINECT 4 methodology

In the KINECT 4 study, eligible patients entered a 48-week treatment period with once-daily INGREZZA followed by a 4-week washout period.[5]



[a]Postbaseline visits during OL treatment period were at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
BL, baseline; OL, open-label; DFWO, drug-free washout.

All patients received INGREZZA 40 mg for 4 weeks. The dosage was then escalated to 80 mg once daily based on individual patient tolerability and clinical response to be reflective of real-world care.[5]

- At the end of Week 4 (first postbaseline visit), patients were escalated to 80 mg if both of the following conditions were met: (1) Clinical Global Impression of Change-TD (CGI-TD) score of ≥3 and (2) acceptable safety and tolerability with 40 mg, based on investigator's judgment[5]
- A dose reduction to 40 mg was permitted once any time after dose escalation due to tolerability. Patients were discontinued if the 40 mg dose was not tolerated[5]

KINECT 4 allowed patients to maintain the 40 mg dose after 4 weeks based on tolerability and treatment response[5]

- 27.6% of patients were maintained on the 40 mg dose for tolerability or because they already experienced an adequate response

Assessments[5,b]

SAFETY ANALYSES	EFFICACY MEASURES ASSESSED
• Treatment-emergent adverse events (TEAEs) • Psychiatric status • Treatment-emergent akathisia or parkinsonism • Emergence of suicidal ideation or behavior • 12-lead electrocardiogram (ECG) • Vital signs and laboratory assessments	• Abnormal Involuntary Movement Scale (AIMS) change from baseline[c,d] • Clinical Global Impression of Change-TD (CGI-TD) • Patient Global Impression of Change-TD (PGIC) • AIMS response rates[e]

[b]All study assessments were analyzed descriptively.
[c]AIMS was scored at baseline and at Weeks 8, 12, 24, 36, 48, and 52 by site raters, who were study investigators (generally psychiatrists).
[d]For continuity with earlier valbenazine studies, AIMS was also scored by consensus between 2 central AIMS video raters (movement disorder neurologists) at limited visits (baseline, Week 8 [first visit after dose escalation], and Week 52 [after washout]). Raters were blinded to treatment and study visit.
[e]AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1–7).

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Long-term safety profile

In the KINECT 4 study, the majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation.[5]

Treatment emergent adverse reactions (TEAEs) reported in ≥3% of all patients[5]

Adverse Events	INGREZZA 40 mg (n=163) (%)	All INGREZZA treated[a] (n=153) (%)	INGREZZA 40 mg (n=35) (%)	INGREZZA 80 mg (n=107) (%)
	BL TO WEEK 4	WEEK 4 TO 48		
Urinary tract infection	1.2%	8.5%	8.6%	8.4%
Headache	4.3%	5.2%	5.7%	5.6%
Nasopharyngitis	1.2%	4.6%	2.9%	3.7%
Suicidal ideation	0.6%	4.6%	8.6%	3.7%
Constipation	0.6%	3.9%	5.7%	1.9%
Fall	0.0%	3.9%	2.9%	2.8%
Fatigue	3.7%	3.9%	8.6%	2.8%
Hypertension	0.0%	3.9%	0.0%	3.7%
Somnolence	3.7%	3.9%	0.0%	3.7%
Back pain	0.6%	3.3%	2.9%	2.8%
Dizziness	0.6%	3.3%	0.0%	4.7%

[a]Includes 11 patients who had a dose reduction from 80 mg to 40 mg after Week 4.
BL, baseline.

- After Week 4, <15% of all participants had serious TEAEs (13.7%) or TEAE leading to discontinuation (11.8%)[5]

Psychiatric status generally remained stable during the clinical study.[5]
No clinically important changes in akathisia or parkinsonism.[5]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS

Somnolence and Sedation
INGREZZA can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA is needed after recovery from NMS, patients should be monitored for signs of recurrence.

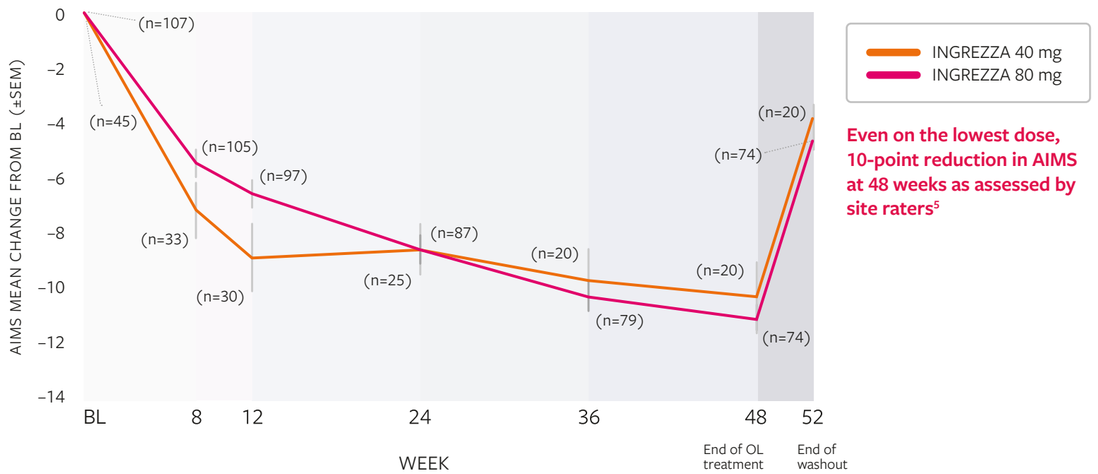
Parkinsonism
INGREZZA may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

Please see Important Safety Information throughout and accompanying INGREZZA full Prescribing Information, including Boxed Warning.

Long-term effectiveness

In the KINECT 4 study, sustained TD improvements were observed with INGREZZA 40 mg. The effectiveness of INGREZZA 80 mg was also studied.[5]

LS mean change from baseline in AIMS dyskinesia total score through 48 weeks (site raters; safety population)[5,a]



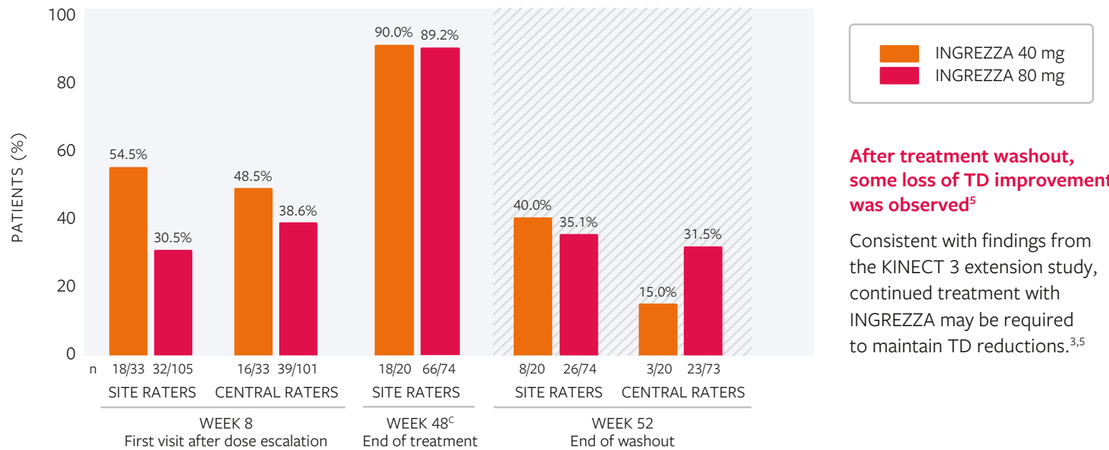
Even on the lowest dose, 10-point reduction in AIMS at 48 weeks as assessed by site raters[5]

In KINECT 4, patients had a dose increase from 40 mg to 80 mg after Week 4, based on CGI-TD score of ≥3 and acceptable safety and tolerability of 40 mg. This was a different dosing schedule than those in KINECT 3 pivotal trial. In KINECT 3, patients in the 80 mg group started on 40 mg and increased to 80 mg after Week 1. The impact of this on long-term effectiveness is not known.

[a]Analyses were based on observed cases, with no imputation of missing data. Data are not shown for 11 participants who had a dose reduction from 80 mg to 40 mg after Week 4.
AIMS, Abnormal Involuntary Movement Scale; BL, baseline; OL, open-label; SEM, standard error of the mean.

- Mean AIMS total score change from baseline to Week 8 was −4.5 for INGREZZA 40 mg and −3.5 for INGREZZA 80 mg, as assessed by central video raters[5]

AIMS score reduction of ≥50% for INGREZZA (site and central raters; safety population)[5,b]



After treatment washout, some loss of TD improvement was observed[5]

Consistent with findings from the KINECT 3 extension study, continued treatment with INGREZZA may be required to maintain TD reductions.[3,5]

[b]AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1–7). Data are not shown for 11 participants who had a dose reduction from 80 mg to 40 mg after Week 4.
[c]Per study protocol, Week 48 AIMS was not evaluated by central AIMS video raters.
AIMS, Abnormal Involuntary Movement Scale.

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KINECT 4: Summary of findings

Long-term treatment with INGREZZA® (valbenazine) capsules 40 mg may be appropriate for some patients

Maintain or adjust back to INGREZZA 40 mg based on your patient's individual treatment needs[5]

For patients who remained on 40 mg, INGREZZA reduced TD severity through 48 weeks[5]

- Even on the lowest dose, 10-point reduction in AIMS at 48 weeks as assessed by site raters
- ~49% and 55% of patients on INGREZZA 40 mg achieved rigorous thresholds of TD improvement at 8 weeks, as measured by AIMS response by central video raters and site raters, respectively[a]

INGREZZA was generally well tolerated long-term with no new safety concerns reported[5]

- Majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation
- Psychiatric stability was generally maintained throughout the study

[a]AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1–7).

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reaction in patients with tardive dyskinesia (≥5% and twice the rate of placebo) is somnolence.

The most common adverse reactions in patients with Huntington's disease (>5% and twice the rate of placebo) are somnolence/lethargy/sedation, urticaria, rash, and insomnia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying INGREZZA full Prescribing Information, including Boxed Warning.

REFERENCES: 1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. **2.** Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174(5):476-484. **3.** Data on file. Neurocrine Biosciences, Inc. **4.** Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017;78(9):1344-1350. **5.** Marder SR, Singer C, Lindenmayer JP, et al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *J Clin Psychopharmacol*. 2019;39(6):620-627.

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